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To Study the Safety and Efficacy of Ivermectin and Doxycycline in Subject of Covid-19

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Abstract: *Introduction and Objective Ivermectin (IVM) and doxycycline (DOXY) have demonstrated in-vitro activity against SARS- management CoV-2, and have a reasonable safety profile. The objective of this systematic review was to explore the evidence in the literature on the safety and efficacy of their use combination therapy in COVID-19 management. Studied a male covid patient, during treatment maximum amount of drugs were given Ivermectin and Doxycycline for about 15 days . When checked after 10 days the patient was notcured successfully. And some of tablets were still in process .While treatment patient was take Ivermectin and Doxycycline high power drugs due to that side effects and interactions were noticed and treatment was started immediately . And the patient was back to normal condition and cured successfully and is healthy.*

Keywords: Ivermectin and Doxycycline

I. INTRODUCTION

What is Pharmacovigilance?

WHO defines Pharmacovigilance as the science and activities relating to the detection, assessment,understanding and prevention of adverse effects or any other possible drug-related problems.

The scope of Pharmacovigilance had grown remarkably and is now considered to include thefollowing domains:

- Medication errors
- Counterfeit or substandard medicines
- Lack of efficacy of medicines
- Misuse and/or abuse of medicines
- Interaction between medicinesObjectives
- To monitor Adverse Drug Reactions (ADRs) in Indian population
- To create awareness amongst health care professionals about the importance of ADRreporting in India
- To monitor benefit-risk profile of medicines
- Generate independent, evidence-based recommendations on the safety of medicines
- Support the CDSCO for formulating safety related regulatory decisions for medicines
- Communicate findings with all key stakeholders
- Create a national center of excellence at par with global drug safety monitoring standards

Components of Pharmacovigilance

- Core Capabilities: Pharmacovigilance delivers four primary capabilities to pharmaceutical companies:
- Adverse Event Case Management including expedited reporting
- Aggregate Reporting
- Signal Intelligence
- Risk Management

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Types of Pharmacovigilance

They may vary in presentation and occurrence and are commonly divided into type A (augmentedpharmaceutical response) and type B (bizarre or hypersensitivity) adverse drug reactions throughout a drug's market life. Pre-marketing safety assessment is generally limited for children.Pharmacovigilance Programme of India (PvPI)

1. Launched by the MoHFW, Govt. of India in the year 2010 at AIIMS New Delhi as NationalCoordinating Centre (NCC).
2. The Programme transferred to IPC as NCC in April, 2011 by a Notification issued by the MoHFW, Govt. of India.
3. IPC-PvPI became the NCC for Materiovigilance Programme of India (MvPI) from July, 2015
4. IPC, NCC-PvPI became a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes & Regulatory services from July, 2017

In India, PvPI is closely working with CDSCO, drug regulatory authority of India. CDSCO understands that Pharmacovigilance plays a specialized and pivotal role in ensuring ongoing safetyof medicinal products in India and it seeks inputs from NCC before taking any kind of regulatorydecisions. NCC-PvPI is working in close coordination with CDSCO zonal offices also for technical, administrative, and logistics matters related to PvPI. The role of NCC in collaboration with other national and international organizations to promote patients safety is illustrated

List of ADR monitoring centers under pharmacovigilance programme of India

Table 1 List of ADR monitoring centres

Sr. No.	Address	Coordinators
1	Department of Pharmacology, All India Institute of Medical Sciences, New Delhi.	Dr. Y.K. Gupta National Coordinator
1.	Department of Pharmacology, & Therapeutics & Toxicology, Govt. Medical College, BakshiNagar, Jammu.	Dr. Vishal Tandon
2.	Department of Pharmacology, PGIMER,Chandigarh	Dr. Bikash Medhi
3.	Department of Pharmacology, R.G. KarMedical College, Kolkatta	Dr. Anjan Adhikari
4.	Department of Pharmacology, Lady Hardinge Medical College, New Delhi	Dr. H.S. Rehan
5.	Department of Clinical Pharmacology, Seth GS Medical College & KEM Hospital, Parel,Mumbai	Dr. Urmila Thatte
6.	Department of Clinical & Experimental Pharmacology, School of Tropical Medicine,Chittaranjan Avenue, Kolkata	Dr. Santanu Tripathi
7.	Department of Pharmacology, JIPMER,Pondicherry	Dr. C Adithan
8.	Department of Clinical Pharmacy, JSSMedical College Hospital, Karnataka	Dr. Parthasarathi G
9.	Department of Pharmacology, MedicalCollege, Guwahati. Assam	Dr. Mangala Lahkar
10.	Institute of Pharmacology, Madras MedicalCollege, Chennai	Dr. R Nandini
11.	Department of Pharmacology, SAIMS Medical College, Indore-Ujjain	Dr. Chhaya goyal
12.	Department of Pharmacology, GSVM MedicalCollege, Swaroop Nagar, Kanpur, U.P.	Dr SP Singh

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13.	Department of Pharmacology, Pandit BhagwatDayal Sharma, Post Graduate Institute of Medical Sciences, Rohtak, Haryana.	Dr MC Gupta
14.	Department of Pharmacology, Dayanand Medical College and Hospital, Ludhiana,Punjab	Dr. Sandeep Kaushal
15.	Department of Clinical Pharmacology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, J&K.	Dr. ZA Wafai
16.	Himalayan Institute of Medical Sciences,Dehradun, Uttrakhand	Dr. DC Dhasmana
17.	Department of Pharmacology, SantoshMedical University, Santosh Nagar, Ghaziabad	Dr VC Chopra
18.	Department of Pharmacology, SMS MedicalCollege , Jaipur	Dr. Mukul Mathur
19.	Department of Clinical Pharmacology, Christian Medical College, Vellore, TamilNadu	Dr. Sujith chandy

Table 2 Functions of Stakeholders

Functions of the Stakeholders	
PvPI ADR Monitoring Centre in Medical College (PvPI AMCs)	Collection of ADR reports Perform follow up with the complainant tocheck completeness as per SOPs Data entry into Vigiflow Reporting to PvPI National Coordinating Centre (PvPI NCC) through Vigiflow Training/ sensitization/ feedback to physicians through newsletters circulated by the PvPI NCC
PvPI ADR Monitoring Centre other than medical colleges [Corporate hospitals, autonomous institutes, public health programmes]	Collection of ADR reports Perform follow up with the complainant to check completeness as per SOPs Report the data to CDSCO HQ
PvPI National Coordinating Centre (PvPI NCC, AIIMS, New Delhi)	Preparation of SOPs, guidance documents & trainingmanuals Data collation, Cross-check completeness, Causality Assessment etc as per SOPs Conduct Training workshops of all enrolled centers Publication of Medicines Safety Newsletter Reporting to CDSCO Headquarters Analysis of the PMS, PSUR, AEFI data received fromCDSCO HQ
ZONAL/SubzonalCDSCO Offices	Provide procurement, financial and administrative support to ADR monitoring centers Report to CDSCO HQ
CDSCO, HQ, New Delhi	Take appropriate regulatory decision & actions on the basis of recommendations of PvPI NCC – AIIMS. Propagation of medicine safety related decisions tostakeholders Collaboration with WHO-Uppsala Monitoring Center -Sweden

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International Conference on Harmonization (ICH) E2e Guideline

Safety specification:

The Safety Specification should be a summary of the important identified risks of a drug, important potential risks, and important missing information. It should also address the populationspotentially at-risk (where the product is likely to be used), and outstanding safety questions whichwarrant further investigation to refine understanding of the benefit-risk profile during the post- approval period. This Safety Specification is intended to help industry and regulators identify any need for specific data collection and also to facilitate the construction of the Pharmacovigilance Plan. The Safety Specification can be built initially during the pre-marketing phase and, at the time approval is sought, it should reflect the status of issues that were being followed duringdevelopment.

The Common Technical Document (CTD), especially the Overview of Safety Benefits and Risks Conclusions and the Summary of Clinical Safety sections, includes information relating to the safety of the product, and should be the basis of the safety issues identified in the Safety Specification. Sponsors should support the Safety Specification with references to specific pages of the CTD or other relevant documents. The Safety Specification can be a stand-alone document,usually in conjunction with the Pharmacovigilance Plan, but elements can also be incorporated into the CTD. The length of the document will generally depend on the product and its development program. Appendices can be added if it is considered important to provide a more detailed explanation of important risks or analyses.

Elements of Safety Specifications:

It is recommended that sponsors follow the structure of elements provided below when compiling the Safety Specification. The elements of the Safety Specification that are included areonly a guide. The Safety Specification can include additional elements, depending on the nature of the product and its development program. Conversely, for products already on the market withemerging new safety concerns, only a subset of the elements might be relevant. The focus of the Safety Specification should be on the identified risks, important potential risks, and important missing information. The following elements should be considered for inclusion.

Non-Clinical:

- Within the Specification, this section should present non-clinical safety findings that have not beenadequately addressed by clinical data, for example:
- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity,hepatotoxicity, genotoxicity, carcinogenicity etc.);
- General pharmacology (cardiovascular, including QT interval prolongation; nervous system;etc.);
- Drug interactions;
- Other toxicity-related information or data.

If the product is intended for use in special populations, consideration should be given to whetherspecific non-clinical data needs exist.

Clinical:

Limitations of the Human Safety Database:

Limitations of the safety database (e.g., related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Particular reference should be made to populations likely to be exposed during the intended or expected use of the product in medical practice.

The world-wide experience should be briefly discussed, including:

- The extent of the world-wide exposure;
- Any new or different safety issues identified;
- Any regulatory actions related to safety.

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Populations not Studied in the Pre-Approval Phase

The Specification should discuss which populations have not been studied or have only been studied to a limited degree in the pre-approval phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed (CTD 2.5.5).Populations to be considered should include (but might not be limited to):

- Children;
- The elderly;
- Pregnant or lactating women;
- Patients with relevant co-morbidity such as hepatic or renal disorders;
- Patients with disease severity different from that studied in clinical trials;
- Sub-populations carrying known and relevant genetic polymorphism;
- Patients of different racial and/or ethnic origins.

Pharmacological Class Effects:

The Safety Specification should identify risks believed to be common to the pharmacologicalclass.

Identified and Potential Interactions, Including Food-Drug and Drug-Drug Interactions:

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. For each, the evidence supporting the interaction and possible mechanism should be summarized, and the potential health risks posed for the different indications and in the different populations should be discussed.

Identification and evaluation of risks including drug-drug interactions and drug-food interactions:

Discussion of risk factors and potential mechanisms that apply to identified AEs/ADRs should draw on information from any part of the CTD (non-clinical and clinical) and other relevant information, such as other drug labels, scientific literature, and post marketing experience.

Identified risks that require further evaluation:

More detailed information should be included on the most important identified AEs/ADRs, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the product. This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at- risk groups, if available. Risk factors and potential mechanisms should be discussed. These AEs/ADRs should usually call for further evaluation as part of the Pharmacovigilance Plan (e.g., frequency in normal conditions of use, severity, outcome, at-risk groups, etc.).

Potential risks that require further evaluation:

Important potential risks should be described in this section. The evidence that led to the conclusion that there was a potential risk should be presented. It is anticipated that for any important potential risk, there should be further evaluation to characterize the association.

Design and Conduct of Observational Studies:

Carefully designed and conducted pharmacoepidemiologic studies, specifically observational (non-interventional, non-experimental) studies, are important tools in pharmacovigilance. In observational studies, the investigator “observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice.”1

Before the observational study that is part of a Pharmacovigilance Plan commences, a protocol should be finalized. Experts from relevant disciplines (e.g., pharmacovigilance experts, pharmacoepidemiologists and biostatisticians) should be consulted. It is recommended that the protocol be discussed with the regulatory authorities before the study starts. It is also suggested that the circumstances in which a study should be terminated early be discussed with regulatory authorities and documented in advance. A study report after completion, and interim reports if appropriate, should be submitted to the authorities according to the milestones within the Pharmacovigilance Plan.

Study protocols should, minimum, include the study aims and objectives, the methods to be used, and the plan for analysis. The final study report should accurately and completely present the study objectives, methods, results, and the

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principal investigator's interpretation of the finding

It is recommended that the sponsor follow good epidemiological practice for observational studies and also internationally accepted guidelines, such as the guidelines endorsed by the International Society for Pharmacoepidemiology. In some of the ICH regions, local laws and guidelines also apply to the design and conduct of observational studies and should be followed.

The highest possible standards of professional conduct and confidentiality should always be maintained and any relevant national legislation on data protection followed

II. DISEASE INTRODUCTION

2.1 What is COVID-19

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. Most people infected with the virus will experience mild to moderate respiratory illness and recover without requiring special treatment. However, some will become seriously ill and require medical attention. Older people and those with underlying medical conditions like cardiovascular disease, diabetes, chronic respiratory disease, or cancer are more likely to develop serious illness. Anyone can get sick with COVID-19 and become seriously ill or die at any age.

The best way to prevent and slow down transmission is to be well informed about the disease and how the virus spreads. Protect yourself and others from infection by staying at least 1 metre apart from others, wearing a properly fitted mask, and washing your hands or using an alcohol-based rub frequently. Get vaccinated when it's your turn and follow local guidance.

The virus can spread from an infected person's mouth or nose in small liquid particles when they cough, sneeze, speak, sing or breathe. These particles range from larger respiratory droplets to smaller aerosols. It is important to practice respiratory etiquette, for example by coughing into a flexed elbow, and to stay home and self-isolate until you recover if you feel unwell.

2.2 Long-term Effects

Most people who have coronavirus disease 2019 (COVID-19) recover completely within a few weeks. But some people — even those who had mild versions of the disease — continue to experience symptoms after their initial recovery.

These people sometimes describe themselves as "long haulers" and the conditions have been called post-COVID-19 syndrome or "long COVID-19." These health issues are sometimes called post- COVID-19 conditions. They're generally considered to be effects of COVID-19 that persist for more than four weeks after you've been diagnosed with the COVID-19 virus.

Older people and people with many serious medical conditions are the most likely to experience lingering COVID-19 symptoms, but even young, otherwise healthy people can feel unwell for weeks to months after infection. Common signs and symptoms that linger over time include:

- Fatigue
- Shortness of breath or difficulty breathing
- Cough
- Joint pain
- Chest pain
- Memory, concentration or sleep problems
- Muscle pain or headache
- Fast or pounding heartbeat
- Loss of smell or taste
- Depression or anxiety
- Fever
- Dizziness when you stand
- Worsened symptoms after physical or mental activities

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Burden of Covid-19

SARS-CoV-2 has caused a devastating pandemic with serious consequences for global health and economy. Globally, as of 18 March 2021, there have been 120,915,219 confirmed cases of COVID-19, including 2,674,078 deaths. The virus is highly transmissible with a basic reproduction number approximately equal to 2.5, and during the first 15 months of its expansion, the virus has caused several pandemic waves across different geographic areas. The risk of severe disease increases significantly with age, and the central focus of public health measures is to reduce SARS-CoV-2 transmission and fatality of the disease. This aim will be accomplished by keeping the case burden of COVID-19 patients within the treatment capacity of the healthcare system. Therefore, it is of importance to know the burden of COVID-19 and COVID-19-related diseases, as well as the healthcare burden

Types of Covid-19

There are fourTrusted Source subtypes of coronavirus — alpha, beta, gamma, and delta —and scientists use these classifications to categorize the various species.

These four coronaviruses typically Trusted Source cause mild respiratory illnesses, such as the common cold, in humans. They are:

- 229E
- NL63
- OC43
- HKU1

These viruses are common worldwide and account for around 15–30%Trusted Source of all common colds. They rarely spread to the lower respiratory tract.

SARS-CoV

This virus causes severe acute respiratory syndrome, or SARS. The first cases of this disease in humans occurred in the Guangdong province of China in 2002Trusted Source.

In total, SARS spread across 26 countries, causing an epidemic with more than 8,000 cases. Since 2004, there have been no recorded cases of SARS in humans. The symptoms of SARS include:

- A fever
- Tiredness
- Chills
- Muscle aches
- A cough
- Difficulty breathing
- Diarrhea

In severe cases, SARS causes a lack of oxygen in the blood, leading to death in 10% of people.

MERS-CoV

This coronavirus causes Middle East respiratory syndrome, or MERS. The first cases occurred in Saudi Arabia in 2012 Trusted Source. Approximately 3 or 4 of every 10 peopleTrusted Source with confirmed MERS dies of the disease.

A 2019 report from the World Health Organization (WHO) suggests that MERS-CoV may spread through contact with animals, particularly camels. Human-to-human transmission is also possible during close contact with people who are sick. Healthcare workers, for example, may be particularly vulnerable.

MERS causes:

- A fever
- A cough
- Shortness of breath

Since 2012, most cases of MERS have occurred in the Middle East. There have been 2,494 casesTrusted Source and 858 deaths.

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No vaccines or drugs can treat or prevent MERS, and health authorities continue to monitor the virus closely.

SARS-CoV-2

SARS-CoV-2 is the virus that causes COVID-19. The first cases of COVID-19 were identified in the city of Wuhan, China, in 2019.

The illness can cause mild to severe symptoms. People with underlying medical conditions and older adults are most at risk of severe COVID-19.

Common symptoms include:

- A fever
- A cough
- Chills
- Body aches
- Headaches
- A new loss of taste or smell
- A sore throat
- Nausea and vomiting
- Diarrhea
- Difficulty breathing

Not everyone with COVID-19 develops all of these symptoms — a person may only have one or two. Also, some people with the disease experience very mild symptoms, while others experience none at all.

Doctors are still learning the best ways to treat COVID-19. Meanwhile, the European Medicine Agency has endorsed the use of dexamethasone for people who need oxygen or ventilation and the Food and Drug Administration (FDA)Trusted Source have also authorized the use of remdesivir for people requiring hospital care.

Major multinational efforts are underwayTrusted Source to develop a vaccine to prevent infections causing COVID-19.

Diagnosis of Covid-19:

- RT-PCR test. Also called a molecular test, this COVID-19 test detects genetic material of the virus using a lab technique called reverse transcription polymerase chain reaction (RT- PCR). A fluid sample is collected by inserting a long nasal swab (nasopharyngeal swab) into your nostril and taking fluid from the back of your nose or by using a shorter nasal swab (mid-turbinate swab) or a very short swab (anterior nares swab) to get a sample. In some cases, a long swab is inserted into the back of your throat (oropharyngeal swab), or you may spit into a tube to produce a saliva sample.
- Results may be available in minutes if analyzed onsite or a few days or longer in locations with test processing delays if sent to an outside lab. RT-PCR tests are very accurate when properly performed by a health care professional, but the rapid test can miss some cases.
- Antigen test. This COVID-19 test detects certain proteins in the virus. Using a long nasal swab to get a fluid sample, some antigen tests can produce results in minutes. Others may be sent to a lab for analysis.

Overview of doxycycline and Action:

Reports from in vitro studies suggest that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host's antiviral response.

Active ingredient	Dosage form	Strength	Proprietary name
Doxycycline	Capsule; delayed release	40 mg	Oracea
Doxycycline monohydrate	Capsule	50 mg, 75 mg, 100 mg	Monodox
Doxycycline hyclate	Capsule	50 mg, 100 mg	Vibramycin
Doxycycline monohydrate	Suspension	25 mg/5 mL	Vibramycin
Doxycycline calcium	Suspension	50 mg/5 mL	Vibramycin
Doxycycline hyclate	Capsule; delayed release	75 mg, 100 mg	N/A
Doxycycline hyclate	Tablet	20 mg	Periostat
Doxycycline hyclate	Tablet	100 mg	Vibra-tabs
Doxycycline hyclate	Tablet; delayed release	75 mg, 100 mg, 150 mg	Doryx

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Drug Interactions between glimepiride and metformin

Interactions between your drugs Doxycycline - Ivermectin

The antiviral and anti-inflammatory properties of ivermectin combined with doxycycline may be beneficial in the treatment of COVID 19. Given that these two drugs have different modes of action, their synergistic effects may contain viral infection by targeting different sites of disease pathogenesis

Drug and food interactions

Doxycycline- Food

If your stomach becomes upset when you take doxycycline, you may take it with food or milk. However, taking doxycycline with milk or food may decrease the amount of medication absorbed from your stomach

Ivermectin - Food

Take ivermectin on an empty stomach, at least 1 hour before or 2 hours after a meal. Ivermectin is usually given as a single dose. Take this medicine with a full glass of water. To effectively treat your infection, you may need to take ivermectin again several months to a year after your first dose.

III. SELECTION OF DRUG CLASS

Antiparasitic

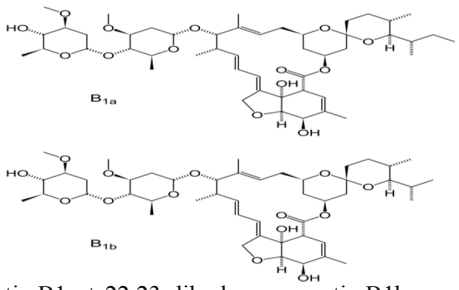
Antiparasitic drugs are a group of medications used in the management and treatment of infections by parasites, including protozoa, helminths, and ectoparasites. Antiparasitic drugs include several classes of drugs that cover a broad range of diseases caused by parasites.

IV. SELECTION OF DRUG

Drug

Ivermectin

Structure



IUPAC Name: -22,23-dihydroavermectin B1a + 22,23-dihydroavermectin B1b

Molecular Formula: -C48H74O14 Molecular weight: -875.1

Mechanism of Action: - Reports from in vitro studies suggest that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host's antiviral response

Side effects:-Tiredness, Loss of energy, Stomach pain, Loss of appetite, Nausea, Vomiting, Diarrhea, Dizziness.

V. LITERATURE REVIEW

Ivermectin

Trial Summary:

Trial ID - NCT04646109

Recruitment information

- Actual Enrollment ICMJE- (submitted: January 25, 2021) 66
- Original Actual Enrollment ICMJE- (submitted: November 25, 2020) 60
- Condition: - Covid 19

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Outcome measures

Control group:-Patients who were hospitalized with a pre-diagnosis of severe COVID-19 pneumonia and thereafter diagnosis of COVID-19 was also confirmed microbiologically with PCR positivity in respiratory tract samples were included into the study. They were randomized to the control and study group, respectively. Hydroxychloroquine, favipiravir and azithromycin (HFA) standard treatment protocol were given to the control group as recommended in the "COVID-19 (SARS-CoV-2 Infection) Guide" prepared by the Republic of Turkey Ministry of Health

Study group :-In addition to HFA treatment, ivermectin 200 micrograms/kg/day (9mg between 36-50 kg, 12mg between 51-65 kg, 15mg between 66-79 kg and 200 micrograms/kg in > 80 kg) in the form of a solution prepared for enteral use was added (HFA+I) to the treatment protocol of the study group's for five days. Blood sample was taken with the first dose of ivermectin and haplotype analysis was performed in ABCB1 and CYP3A4 genes in the whole study group. Ivermectin: Ivermectin 5mg/5ml solution was manufactured by NEUTEC™ Pharmaceutical Company-Turkey, under "Good Manufacturing Practices" (GMP) certification conditions.

Primary Outcome 1:

Table 3 Gender distribution of patient in Ivermectin trial

Arm/Group Title	Control Group	Study group
Male	19	21
Female	11	9
Total	30	30

Primary Outcome 2:

Table No.4 Percentage of Patients with Accompanying Diseases

Arm/Group Title	Control Group	Study group
Overall Number of Participants Analyzed	30	30
Diabetes mellitus	10	9
Hypertension	12	15
Coronary artery disease	8	5
Cardiac failure	1	0
;Chronic obstructive	3	6
Malignancy	1	0
Immunodeficiency	1	0

Primary Outcome 3: -

Table No.5 Percentage of Patients With Baseline Clinical Symptoms

Arm/grp title	Control Group	Study group
Fever	13	15
Cough	14	16
Sour throat	1	3
Dyspnea	19	23
Headache	2	5
Weakness	11	13
Myalgia	7	9
Diarrhea	0	1
Nausea	0	1
Total	30	30

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Secondary outcome 1 :-

Table No. 6 Number of Participants with Clinical Response and mortality

Arms/grp title	Control Group	Study group
Overall Number of Participants Analyzed	30	30
Measure Type: Count ofParticipants Unit of Measure: Participants	16	22
Mortality	9	6

Secondary outcome 2:-

Table No. 7 Changes in Oxygen Saturation (SpO2) Values

Arm/grp Title	Control Group	Study grp
Overall Number of Participants Analyzed	30	30
Baseline	89.67 (5.09)	89.93 (6.51)
FD1	92.43 (2.86)	94.54 (2.21)
FD3	92.91 (2.71)	94.24 (2.76)
FD5	93.00 (3.93)	95.35 (2.72)

Secondary outcome 3:-

Table No. 8 Changes in Serum Ferritin Levels

Ars/grp Title	Control Group	Study grp
Overall Number of Participants Analyzed	30	30
Baseline	747.05 (800.54)	682.75 (470.08)
FD1	1076.88 (704.05)	628.45 (580.10)
FD3	1097.57 (595.22)	433.48 (641.82)
FD5	1206.90 (782.84)	494.71 (349.78)

Overall Study

Table 9 Overall study of Ivermectin

Started	30	36
Completed	30	30
Not completed	0	6
Reason not completed		
Mutation disrupting ivermectin metabolism was found in6 patients	30	30

Arms and Intervention

Table No. 10 Arms and Intervention of Ivermectin

Arm/GroupTitle	Control Group	Study Group	Participants WithMutations
Arm/Group Description	Patients who were hospitalised with a pre-diagnosis of severe COVID-19 pneumonia and thereafter diagnosis of COVID-19 was also confirmed microbiologically with	In addition to HFA treatment, ivermectin 200 micrograms/kg/day (9mg between 36-50 kg, 12mg between 51-65 kg, 15mg between 66-79 kg and 200 micrograms/kg in > 80 kg) in the form of a solution	Patients that were included in the study group and excluded from the study because one or both of the multidrug resistance 1 (MDR1) / ABCB1 and CYP3A4 genes were

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	PCR positivity in respiratory tract samples were included into the study.	prepared for enteral use was added (HFA+I) to the treatment protocol of the study group's for five days..	detected in the blood sample taken at the beginning of ivermectin treatment on the first day

Adverse event

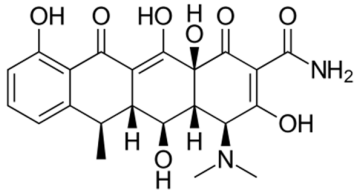
Table No. 11 Adverse event of Ivermectin

AEs	Control Group	Study Group	Participants WithMutations
Serious adverse event	0/30 (0.00%)	0/30 (0.00%)	5/6 (83.33%)
Other adverse events	3/30 (10.00%)	0/30 (0.00%)	0/6 (0.00%)
All cause mortality	9/30 (30.00%)	6/30 (20.00%)	0/6 (0.00%)

Antibiotics

Antibiotics are medicines used to prevent and treat bacterial infections. Antibiotic resistance occurs when bacteria change in response to the use of these medicines. Bacteria, not humans or animals, become antibiotic-resistant

Doxycycline



IUPAC Name: -4S,4aR,5S,5aR,6R,12aS)-4-(Dimethylamino)-3,5,10,12,12a-pentahydroxy-6- methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide

Molar mass: -444.440 g·mol−1Formula: $C_{22}H_{24}N_2O_8$ Mechanism Of Action

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gramnegativebacteria

Side effects: Diarrhea, Difficulty swallowing, Drug rash., Esophageal ulcer, Esophagitis, Facialredness, Headache, Hives.

Ivermectin and DoxycyclineTrial ID - NCT04523831

Study Design

- Study Type:- Interventional (Clinical Trial)
- Actual Enrollment:-400 participants
- Allocation:- Randomized
- Intervention Model:- Parallel Assignment
- Intervention Model Description: Patient will be randomized 1:1 to placaebo withstandard care and combined doxycycline and ivermectin with standard care.
- Masking: Double (Participant, Investigator)
- Masking Description: Double blind (The participant and the clinicians/data collectors willbe unaware of the treatment the participant receives).The drugs will be labelled with a random code number
- Primary Purpose: Treatment. Official Title: A Phase III Trial to Promote Recovery From Covid 19 With Combined Doxycycline and Ivermectin Along Standard Care

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Outcome measures

Table 12 Outcome Measures of Ivermectin and Doxycycline

Arm/Group Title	Ivermectin PlusDoxycycline	Placebo
Overall Number of Participants Analyzed	183	180
Early Clinical Improvement	111	80
Late Clinical Recovery	42	67
Clinical Deterioration.	16	32
Positive for RT-PCR ofCovid-19	14	36

Arms and Interventions

Table 13 Arms and Intervention of Ivermectin and Doxycycline

Arms	Intervention
Active Comparator: Ivermectin andDoxycycline Ivermactin 6 mg 2 tab stat, cap Doxycycline100 mg 1 cap BD 5 days	Drug: Ivermectin and Doxycycline Ivermectin 6 mg, 2 tab stat and Doxycycline100 mg twice daily for 5 days Other Name: Imac and Doxibac
Placebo Comparator: PlaceboStandard treatment	Drug: Standard of care Paracetamol, Vitamin D, Oxygen if indicated, Low molecular weight heparin,dexamethasone if indicated

Overall study

Table No. 14 Overall study of Ivermectin and Doxycycline

Arm/Group Title	Ivermectin and Doxycycline	Placebo
Started	200	200
Not completed	17	20
Lost in follow up	15	17
Death	0	3
Adverse event	2	0

Adverse event

Table no. 15 Adverse event of Ivermectin and Doxycycline

Arm/Group Title	Ivermectin andDoxycycline	Placebo
All-cause mortality	00/183 (0.00%)	03/180 (1.67%)
Serious adverse event	02/183 (1.09%)	00/180 (0.00%)
Other serious adverseevent	07/183 (3.83%)	0/180 (0.00%)

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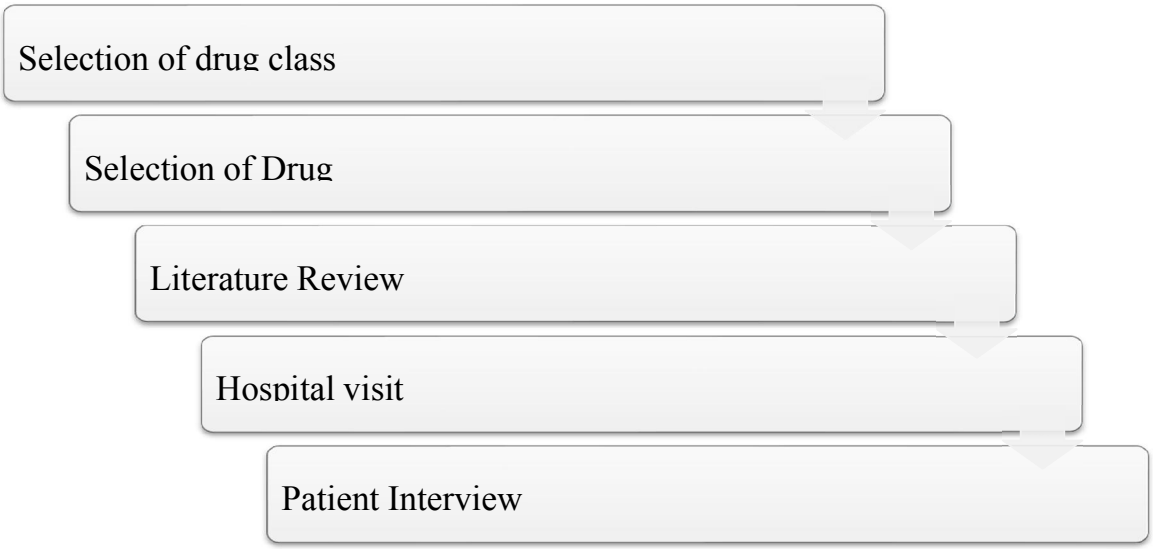
VI. PLAN OF WORK



CASE REPORT

Personal information:-
Name of pateint:- xyz
Age:- 42.
Gender:- male
Weight :-79 kg
Diagnosis:- COVID-19 RT-PCR
Specimen – Nasopharyngeal/ Oropharyngeal swabCOVID-19 Qualitative PCR – Positive

Table No. 16 Result of Swab Test

Target genes	Detected /not detected	CT value
ORF1 ab genes	Detected	17
N gene	Detected	18
RNaseP gene	Detected	21

BLOOD EXAMINATION REPORT

Table No. 17 Blood Reports

Test	Observed	Normal
Hemoglobin	12.1gm%	In male - 13.5 to 18gm%

C.T SCAN OF THORAX PLAIN

- Transaxial helical multislice spiral CT scan of Thorax has been performed on MDCT scanner
- Multifocal patchy peripheral sub-pleural areas of ground glass densities and consolidations arescattered in both Lungs .
- Rests of the lung parenchyma is unremarkable. No mediastinal mass or lymphadenopathy isdetected.
- Tracheo Bronchial tree is normal.The mediastinal vascular structures appear normal.
- The pleural spaces are clear.Bony thorax is unremarkable.Both the axillary spaces are clear
- CT severity index with involvement of each lobe is as follows: Right upper lobe: <5%-1
- Right middle lobe:<5%-1, Right lower lobe:5-25%-2, Left Upper lobe:5-25%-2, Left lowerLobe:5-25%-2

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Impression: Multifocal patchy peripheral sub-pleural areas of ground glass densities are scatteredin both lungs with patchy areas of consolidations – Findings are s/o atypical viral pneumonia, CTseverity scoring is 8 out of 25. CORADS-

Treatment and prescription

Day 1 :- TPR (temperature, pulse, respiration: used especially in recording a patient's vital signs on a medical chart.)/BP (blood pressure measuring device)/Io charting(The Full form of I-O is Input-Output, or I-O stands for Input-Output, or the full name of given abbreviation is Input- Output.)

1. Inj. Pipzo 4.5 IV bd
2. Inj.pan 40mg IV bd
3. Inj. Lamoh 0.4 IV od
4. Tablet fabiflu 400mg 9tablet for day1
5. Tab. Mucinac 600 bd
6. Tab.Ivermectin od
7. Tab.Rabera-DSR bd
8. Tab. Oxy bd
9. Tab vit c bd
10. Tab vit d3 od
11. Tab. calpol 650
12. Tab. Azee 500 od

Day 2:- TPR/BP/Io charting

1. Inj. Pipzo 4.5 IV bd
2. Inj.pan 40mg IV bd
3. Inj.clexane 0.4od
4. Dexa 2cc IV bd
5. C.T all

Day 3:- TPR/BP/Io charting

1. Inj. Pipzo 4.5 IV bd
2. Inj.pan 40mg IV bd
3. Inj.clexane 0.4 od
4. Dexa 2cc IV bd
5. C.T all

Day 4: TPR/BP/Io charting

1. Inj. Pipzo 4.5 IV bd
2. Inj.pan 40mg IV bd
3. Inj. Clexane 0.4 od
4. C.T all

Day 5: TPR/BP/Io charting

1. Inj. Pipzo 4.5 IV bd
2. Inj. Pan 40mg iV bd
3. Inj. Clexane 0.4 od
4. C.T all

Adverse events: -

- Nausea
- Vomiting

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- Fatigue
- Alopecia
- Drowsiness

Treatment of adverse event:-
Tab. Calpol 650
Tab. Azee 500
Tab Vit D3 Vit c

VII. CONCLUSION

COVID-19 is a serious infection that has led to thousands of cases of severe pneumonia, ARDS, and even deaths across the globe. As of now there are no approved treatments for this viral pandemic. While several medications have shown to be effective in clinical trials, further studies are needed to establish dosing, treatment course, and side effects of these medications. As the number of cases and deaths continue to increase in the world, the race to develop faster testing modalities to rapidly diagnose and manage these patients earlier continues to be the focus of the global healthcare system. The pateints score was low so the patient got cure in 5 days.

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